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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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NGUYEN,Q	
ART UNIT	**PAPER NUMBER**
1632	2

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/578,656	Applicant(s) LI ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 12-17, drawn to a method of testing for therapeutic efficacy on spinal muscular atrophy conditions using a transgenic mouse of the instant claimed invention, classified in class 800, subclass 3.

II. Claims 18 and 19, drawn to a method for testing the accuracy and sensitivity of diagnostic methods for spinal muscular atrophy using a transgenic mouse of the instant claimed invention, classified in class 800, subclass 3.

Claims 1-11 are drawn to a transgenic mouse model for spinal muscular atrophy and a method of generating the same, classified in class 800, subclasses 18, 22, 25, for examples, will be examined with the elected group.

The inventions are distinct, each from the other because of the following reasons:

Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Groups I and II are directed to methods that are distinct both physically and functionally, with different endpoints and are not required one for the other. Invention I requires the testing for the therapeutic efficacy of gene and drug therapies on spinal muscular atrophy conditions using a transgenic mouse model. Invention II requires the testing of accuracy and

sensitivity of diagnostic methods for spinal muscular atrophy using a transgenic mouse model.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone discussion with Attorney Kent H. Cheng on August 15, 2000, a provisional election was made without traverse to prosecute the invention of group I. Affirmation of this election should be made by applicant in replying to this Office action.

Group II is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being for a nonelected invention.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the use of "said mouse model". Correction is required. See MPEP § 608.01(b).

Sequence compliance

The disclosure is objected to because of the following informalities: The specification contains sequence listings. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

For a complete response to this office action, applicant must submit the required material for sequence compliance.

Claim Objections

Claim 9 is objected to because of the following informalities: "phosphoribosyl-transerase" is misspelled, it should be - - phosphoribosyl transferase - -. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a disruption in both alleles of endogenous *Smn* gene, wherein disruption is generated by targeted replacement with a non-functional *Smn* gene, and whose genome comprises at least one human genomic DNA sequence comprising a human SMN^c region with centromeric SERF1 and part of centromeric NAIP, and wherein said mouse has a wide range of symptons, from early death to abnomalities comprising a significant loss of large motor neurons in the anterior horns, a decrease in muscular fiber, atrophic muscular bundles and subcutaneous edema in the tail tissue compared to normal or heterozyous $Smn^{+/-}SMC^c$ mouse, a method of generating said transgenic mouse, and a method of testing for therapeutic efficacy on spinal muscular atrophy conditions using the same transgenic mouse, does not reasonably provide enablement for a transgenic mouse model for human spinal muscular atrophy in which the genome for the transgenic mouse comprises at least one mutation that reduces the native mouse *Smn* gene expression and whose genome further comprises at least one human genomic DNA sequence wherein the expression of the DNA sequence compensates for the reduced expression of said *Smn* gene, a method of generating said mouse model and a method of testing for therapeutic efficacy on spinal muscular atrophy conditions using the same mouse model. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 1-7 are drawn to a transgenic mouse model in which the genome of the transgenic mouse comprises at least one mutation that reduces expression of the native mouse *Smn* gene, and whose genome further comprises at least one human genomic DNA sequence, wherein the expression of the DNA sequence compensates for the reduced expression of said *Smn* gene. Claims 8-11 are directed to a method of generating the same transgenic mouse model, whereas claims 12-17 are drawn to a method for testing therapeutic efficacy on spinal muscular atrophy conditions using the same transgenic mouse model.

The specification discloses vector constructs, and the generation of SMN^c transgenic mouse lines and *Smn* knockout mice. By crossing the F0 SMN^c transgenic founders to $Smn^{+/-}$ knockout mice, F1 mice having the human transgene SMN^c and are heterozygous for the mouse *Smn* locus ($Smn^{+/-}SMN^c$) were obtained. Transgenic mice homozygous for the endogenous knockout *Smn* alleles ($Smn^{-/-}SMN^c$) were generated by F1 crossing with $Smn^{+/-}$ knockout mice or F1 intercrossing. The specification teaches that while heterozygous $Smn^{+/-}SMN^c$ mice showed no gross morphological difference in comparison with normal mice, the $Smn^{-/-}SMN^c$ showed a wide range of symptoms, from

early death to mild abnormalities. Comparing to normal and heterozygote siblings, these mice have lower body weights and shorter tails. Further characterization of these *Smn* $^{-/-}$SMN^{c} mice revealed a decrease in muscular fiber, atrophic muscular bundles and subcutaneous edema mainly in the tail tissue, a significant loss of large motor neurons in the anterior horns was observed in most mice displaying severe symptoms. The human SMN^{c} transgene is expressed extensively in all tissues of the *Smn* $^{-/-}$SMN^{c} mice, the majority of the transcripts lack exon 7 due to alternative splicing with lesser amounts of full length transcript, and transcripts with alternative spliced exon 3 or exon 5. Mice with mild symptoms generally produced more full length transcripts, and more SMN protein.

The above evidence is noted and considered. However, the evidence can not be extrapolated to the instantly broadly claimed invention which when read in light of the specification is drawn to a transgenic mouse model for human spinal muscular atrophy, a method for preparing said transgenic mouse model and a method of testing therapeutic efficacy on spinal muscular atrophy conditions using the same model.

With respect to claims directed to a transgenic mouse model for human spinal muscular atrophy (SMA), it should be noted that the transgenic mouse to be used as a model must have complete complement and symptoms of human spinal muscular atrophy. Although pathological analysis of the tail tissue of *Smn*$^{-/-}$SMN^{c} transgenic mouse revealed a decrease in muscular fiber and atrophic muscular bundles, the presence of atrophic muscle fibers in trunk muscles was generally not detected (See specification, page 22, lines 20-22 to page 23, lines 1-7). Moreover, the significance of

a short and enlarged tail phenotype displayed by said transgenic mouse to human SMA pathology is uncertain. In addition, the specification fails to teach the age of disease onset and functional ability for the three groups of *Smn*$^{-/-}$SMN^{c} transgenic mouse to reflect human SMA types I, II and III (Wong et al., Curr. Opin. Neurobiol. 8: 791-799, 1998, column 1, page 795, second last paragraph). The specification merely recites that "Type I mice, the most severe type, died around day 10 without furry hair development; type II mice showed poor activity and died in 3-4 weeks; and type III mice survived and bred normally but had shorter and enlarged tails." (See specification, page 16, lines 22-23 to page 17, lines 1-2). Nevertheless, *Smn*$^{-/-}$SMN^{c} transgenic mice of the instant claimed invention exhibit neurological defects similar to the pathological features of human SMA patients such as, a significant loss of large motor neurons in the anterior horns with the appearance of empty cell beds with occasional central chromatolysis in some other motor neurons, a marked glial outgrowth, a selective loss of thick myelinated fibres, axonal degeneration in both anterior and posterior spinal roots.

With regard to the breadth of the claims drawn to a transgenic mouse whose genome comprises at least one mutation that reduces expression of the native mouse *Smn* gene and whose genome comprises at least one human genomic DNA sequence, wherein expression of the DNA sequence compensates for the reduced expression of said *Smn* gene, and wherein said transgenic mouse can be used as a model for human spinal muscular atrophy, the specification clearly does not support for such a broadly claimed invention. For example, the instant specification recites on page 16, lines 18-20 that "While the heterozygous *Smn*$^{+/-}$SMN^{c} mice showed no gross morphological

difference in comparison with normal mice, the *Smn*$^{-/-}$SMN^{c} mice showed a wide range of symptoms, from early death to mild abnormalities". It is evident that a single disruption in exon 7 of an endogenous mouse *Smn* allele is not sufficient to produce SMA-like symptoms in the transgenic mouse. In addition, the specification fails to teach or provide guidance and direction for the generation of a transgenic mouse whose genome comprises any and all human genomic DNA sequence whose expression compensates for the reduction of *Smn* gene as a result of a null homozygous smn background, and said transgenic mouse still displays SMA like symptoms. Instead of introducing a human genomic DNA sequence encompassing a human SMN^{c} region into a homozygous *Smn*$^{-/-}$ background mouse as disclosed in this application, would a transgenic mouse with the same background whose genome further comprises a human DNA sequence encompassing a telomeric SMN^{T} region still exhibits SMA like symptoms? Most likely not, because unlike SMN^{c} transcripts which are frequently subjected to alternative splicings, particularly at exon 7, most SMN^{T} transcripts appear full length (Gennarelli et al., Biochem. Biophys. Res. Commun. 213:342-348, 1995, Fricker, DDT 5:220-221, 2000), and the deletion of exon 7 has been attributed to lower levels of SMN protein and as indicated in the instant specification, the severity of the disease is correlated to a decrease in the amount of SMN protein (page 20, lines 13-16). As such, the expression of full length SMN^{T} transcripts would fully rescue a transgenic mouse with a homozygous *Smn*$^{-/-}$ background from any SMA phenotype. Even mice with a homozygous null *Smn* allele background having sufficiently high copy

number of SMN^c gene have normal phenotype (Monani et al., Hum. Mol. Genet. 9:333-339, 2000).

Regarding to the claims drawn to a transgenic mouse model wherein said mouse model genotypically and phenotypically mimicks human spinal muscular atrophy patients, the specification fails to provide guidance or direction and example for one skilled in the art to make and use such a model. The disclosed *Smn*$^{-/-}$$SMN^c$ transgenic mouse exhibiting neurological defects similar to pathological features observed in human SMA patients is certainly not genotypically mimicking human SMA patients. This is because the mouse genome is very different from the human genome. Furthermore, the genome of human SMA patients does not comprise a cassette of hypoxanthine phosphoribosyl-transferase. As already discussed above, the disclosed *Smn*$^{-/-}$$SMN^c$ transgenic mouse of the instant claimed invention does not mimick phenotypically entirely to human SMA patients, for example the feature of a short and enlarged tail displayed by the transgenic mouse.

Since the broadly claimed transgenic mouse model for human spinal muscular atrophy is not enabled by the instant specification, the method of generating said transgenic mouse model, and a method of testing for therapeutic efficacy on spinal muscular atrophy conditions using the same are also not enabled.

Accordingly, due to the lack of guidance, direction, and examples provided by the specification for a transgenic mouse model of human spinal muscular atrophy, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-8, 12 and 15 the phrase "transgenic mouse model" is unclear. Is it a model for the disease spinal muscular atrophy or a model for some symptons of said disease? If it is a model for the disease, then such transgenic mouse must have the complete complement and symptoms of the disease.

The terms "substantially" and "partially" in claim 1 are relative terms which render the claim indefinite. The terms "substantially" and "partially" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claims 2, 6 and 7 it is unclear what is encompassed by the phrase "genotypically and phenotypically". How can a transgenic mouse is genotypically mimicking human spinal muscular atrophy patients? For one thing, mouse genome is different from human genome. Furthermore, which symptons in human spinal muscular atrophy patients that the transgenic mouse of the instant claimed invention mimicks? Clarification is needed.

In claim 8, the phrase "said mouse" on line 5 of the claim is unclear. Which mouse? Is it a normal mouse or a mouse with an introduced mutation in the genome resulting in the reduction of mouse Smn gene expression? Clarification is requested.

In claims 12, 14, and 17, it is unclear what is encompassed by the phrase "conditions characteristics of spinal muscular atrophy". Which conditions are considered to be characteristics of spinal muscular atrophy and which ones would not be considered? Clarification is required.

In claims 13 and 16, the phrase "changing genomic DNA sequences" is vague and unclear. Which genomic DNA sequences? The mouse DNA or the human DNA in the transgenic mouse. Furthermore, how is the replacement of genomic DNA sequences carried out? Clarification is requested.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, J.D., may be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Quang Nguyen, Ph.D.

Examiner, AU 1632

Karen M. Hauda

KAREN HAUDA
PRIMARY EXAMINER